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REPORT ON
THE SEMINAR ON JAPANESE ENCEPHALITIS AND
OTHER ARBOVIRUS INFECTIONS

Tokyo, Japan, 5-14 November 1962

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SEMINAR ON JAPANESE ENCEPHALITIS AND
OTHER ARBOVIRUS INFECTIONS

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N O T E

The views expressed in this report are those of the advisers and participants at the Seminar and do not necessarily reflect the policy of the World Health Organization.

This report has been prepared by the Western Pacific Regional Office of the World Health Organization for governments of Member States and for all who participated in the Seminar on Japanese Encephalitis and Other Arbovirus Infections, Tokyo, Japan, 5-14 November 1962.

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The Seminar on Japanese encephalitis and other arthropod-borne virus infections organized by the Western Pacific Regional Office of WHO met in Tokyo from 5 to 14 November 1962. The Japanese Minister of Health and Welfare, Mr. Eiichi Nishimura, welcomed the participants and opened the Seminar. Addresses of welcome were also given by the Governor of Tokyo, Dr. Ryotaro Azuma, the President of the Japanese Association for Medical Science, Dr. Takeo Tamiya and the Vice-President of the Japanese Medical Association, Dr. Tetsuo Abe. A message from the Regional Director of WHO, Dr. I. C. Fang, reviewing some of the more important problems in this field, was read. The Group unanimously elected Professor Yoshio Kawakita as Chairman, Professor Sadari L. Kalra as Vice-Chairman, and Dr. Ian D. Marshall as Rapporteur, and adopted the proposed agenda.

The provisional agenda for the seminar is given in Annex No. 5, the list of participants, observers and secretariat in Annex No. 6 and the list of documents issued in Annex No. 7.

1. INTRODUCTION

There are now some 150 viruses recognized as arthropod-borne animal viruses. Of these, at least 50 are pathogenic for man and four others are of considerable veterinary importance. Among the arboviruses¹ 45 have been shown to occur in the Regions represented at this Seminar and those infecting man are given, together with their geographic distribution, in Annex 1.

Japanese encephalitis is a disease of great importance in many countries in the Regions and various haemorrhagic fevers appear to be increasing in importance. Apart from these dengue is the cause of a considerable amount of sickness and, from time to time, of very large epidemics. There are diseases caused by other viruses present which could, in suitable circumstances, also present a very serious public health problem.

Because of this, and because of the interest shown by some governments in the Region, the Western Pacific Regional Office of WHO organized a seminar with participants from this Region and from South-East Asia with the following objectives:

1. To exchange information in the Western Pacific and South-East Asia Regions.
2. To present in concise form information on the important findings of the extensive research work being done in a number of countries and to discuss the methods of attack on the problems still requiring solution.
3. To consider and discuss the control of these infections.

¹Arbovirus has recently been accepted by the international committee for virus nomenclature as the official name for the arthropod-borne animal viruses.

2. JAPANESE ENCEPHALITIS

2.1 Definition

Japanese encephalitis (JE) is an acute mosquito-borne disease of man, horses, swine fetuses and occasionally other domestic animals such as cattle and goats caused by a group B arbovirus and occurring in South-East Asia and the Western Pacific from Singapore and India, to Japan and eastern U.S.S.R. Over 90% of human and animal JE virus infections are asymptomatic or sufficiently mild to be unrecognizable. In less than 10% of infections, acute encephalitis develops, but in such clinically recognized cases, the mortality rate is commonly 20-50%.

2.2 Public health importance

The important disease caused by JE virus is encephalitis of man and horses. For example, in 1948 in Japan there occurred 4757 human cases with 2620 fatalities (morbidity rate 5.9 per 100 000 and case fatality rate 55.1 percent) and 3678 horse cases (morbidity rate 330 per 100 000). Dissemination of JE virus among domestic animals, horses and swine fetuses can result in serious economic losses. However, except for swine fetuses and piglets (death may take place before at, or shortly after birth), pigs, cattle, goats, sheep and dogs are usually infected only inapparently.

In 1948, JE in Japan was designated a notifiable infectious disease, and vaccination of horses was started. As a result, only 102 of 91 046 vaccinated horses (morbidity rate 112 per 100 000) suffered from encephalitis while 1269 (443 per 100 000) occurred among non-vaccinated. Since 1948 encephalitis in horses has become rare in Japan except in Hokkaido where vaccination is not frequently employed. Vaccination of sows also has produced some good effects in decreasing the incidence of still-births. However, contrary to the results in horses and sows, human cases still occur, roughly 2000 every year. Even though JE vaccine has been authorized to be used since 1954, and allergic encephalomyelitis (a potential danger with mouse brain vaccines) has not been observed among vaccinees and only rarely with experimental animals, vaccine has not been used widely in the Western Pacific Region.

In Japan human case fatality rates are 20-50 percent, much higher in old people, and approximately 20 percent of all survivors have permanent sequelae such as mental defects and physical disorders. Accordingly, intensive efforts should be directed toward preventive measures as described in a subsequent section of this report.

The importance of this disease is not known in many tropical parts of South-East Asia and the Western Pacific where, as explained below under Ecology, epidemics rarely occur. JE virus is known to occur throughout these areas (see Annexes 1, 3 & 4) but its public health importance in many countries needs to be evaluated by confirmatory laboratory diagnostic studies of encephalitis cases.

2.3 Etiological Agent

Among the biological characteristics of JE virus exhibited by "wild" strains from nature are (1) pathogenicity for adult and suckling mice by both intracranial (IC) and intraperitoneal (IP) inoculation, (2) ability to kill cells in cultures of hamster kidney and porcine kidney, and of chicken

embryonic tissues under agar, (3) varying pathogenicity for animals and men, (4) easy production by conventional methods of haemagglutinin which acts over a wide range of pH (optimum about pH 6.5).

Certain variants of the Nakayama strain have little pathogenicity for adult mice by intraperitoneal inoculation and differences in antigenicity have been detected by haemagglutinin absorption techniques. Differences in antigenicity have been observed in virus isolates even from the same area, although all strains of JE virus are more closely related to each other than to other members of the Group B arboviruses including MVE virus. By means of serial passages in various hosts under certain conditions, variants or mutants of JE virus have been selected. Some examples discussed at the Seminar are tabulated below.

TABLE 1

<u>Method of selection</u>	<u>Variation</u>
Primary hamster kidney (HK) cell cultures	Not lethal for adult mice IC and suckling mice subcutaneously (SC)
1-day egg	Reduced lethality for adult mice IC
1-day egg, then HK cell culture	Reduced lethality for adult mice IC, non-immunogenic
1-day egg, then HK cells, clonal selection	Reduced titres in adult mice IC, but immunogenic
Primary embryonic mouse skin cell culture and HK cell culture	6 logs lower pathogenicity IC in adult and SC in suckling mice (M mutant)
Virus heated 50°C for 1 hr. then HK cell culture	Heat resistant, otherwise similar to wild type. (T mutant)
HK cell cultures at 42°C	Higher titres at 42°C, small plaques at 36°C. (RCT/42°C mutant)

2.4 Pathogenesis and clinical manifestations

After introduction into the body and multiplication in viscera, the virus invades and penetrates the endothelial lining of capillaries, especially in the brain. Qualitative and quantitative differences of vascular supply in different parts of the brain appear to determine the distribution of pathological lesions. There are severe and extensive perivascular infiltrations with inflammatory cells, proliferation of glial cells and degeneration of neurons. Inflammation of meninges leads to signs of meningeal irritation and thrombi in blood vessels often occur. An important factor determining severity of clinical manifestations is the amount of oedema in cerebral tissue.

After an incubation period of 4-14 days, the disease usually begins quite acutely with fever, marked and increasing disturbances of the sensorium and signs of meningeal irritation such as neck rigidity and a positive Kernig's sign. Fits are a common presenting symptom in children. Manifestations of motor neuron disease, usually of the upper motor neuron type, and of extra-

pyramidal tract disease are frequent. The cerebrospinal fluid almost invariably shows abnormalities, consisting of mild to moderate pleocytosis, a normal or slightly elevated glucose content, and a moderately raised protein level.

After a week or so, the patient enters into the convalescent phase, with subsidence of fever by lysis and improvement in consciousness and neurological signs.

The mortality ranges from below 10% in endemic areas to 20-50% in severe epidemics. Usually deaths occur in the first few days of illness. Common complications include pneumonia and bedsores. Sequelae also have a variable incidence, ranging from 15-50%, and can be physical, mental, psychological or combinations of these. The sequelae, especially in children, may not be apparent until months or years after the acute stage of illness.

2.5 Ecology and geographic distribution of vectors

Far eastern U.S.S.R.: Culex tritaeniorhynchus is believed to be the important vector. There are, however, seaside and sea-island foci where Aedes togoi is said to transmit the virus. Korea: Virus isolations have been made from C. tritaeniorhynchus and it is believed to be the important vector. Japan: C. tritaeniorhynchus is the proven vector during the epidemic season. The virus has been isolated from Culex pipiens but this mosquito is not considered to be of primary importance. Ryukyu Islands: C. tritaeniorhynchus is believed to be the vector. Numerous virus isolations have been made from this mosquito. Taiwan: The vector in northern Taiwan is C. tritaeniorhynchus. The vector in the southern part of the island has not yet been determined. One isolation, from Culex fuscocephalus, has been made in the latter area. The habits and great abundance of this mosquito suggest that it may be a vector. India: The virus has been isolated from the Culex vishnui complex in Vellore and this mosquito is most probably the vector in that area. C. tritaeniorhynchus may be the vector in the Kashmir valley. Malaya and Singapore: The virus has been isolated from C. tritaeniorhynchus and Culex gelidus, and both species are thought to be important vectors. Hong Kong, Philippines, Guam, Cambodia, Viet Nam and Thailand: The virus has not yet been isolated from mosquitoes in these areas.

C. tritaeniorhynchus is the most widely distributed and probably the most important vector. The larvae are found in rice fields, marshes and small, stable collections of clean water around cultivated fields. It is a warm weather mosquito with peaks of abundance in July, August and September in subtropical and temperate climates. The adult females do not rest in houses or animal shelters in the daytime, except in small numbers in temperate zones. Entry and resting at night in houses and animal shelters have been observed, but feeding probably takes place most often in the open. Feeding activity is greatest during the first hour after sunset. The larger domestic mammals are the preferred hosts but birds and man are also attacked. The other probable vectors, C. vishnui, C. gelidus and C. fuscocephalus have been studied less intensively. Their habits, in general, appear to resemble those of C. tritaeniorhynchus.

2.6 Ecology and geographic distribution of vertebrate hosts

The ecology of JE virus in non-arthropod hosts can be divided into temperate and tropical zone ecology. At the moment the only known non-arthropod hosts of JE virus are vertebrates though it is conceivable that invertebrates other than arthropods might someday be shown to be important hosts.

In temperate zones, JE virus infects vertebrates seasonally, i.e., in the summer when adult female vector mosquitoes exist in sufficient numbers in nature. To date the virus has been detected annually first in vector mosquitoes and is detected in amplifier hosts such as birds of certain species and pigs somewhat later. Amplifier hosts are vertebrates which occur yearly as large numbers of susceptibles and are attractive to vector mosquitoes. Such animals therefore can serve as hosts for virus reproduction following bite of a transmitting mosquito, become viraemic for several days or at least sufficiently long to infect other mosquitoes which ingest blood containing virus. Amplification occurs because an amplifier host can become infected by the bite of only one mosquito, whereas while viraemic, it can infect hundreds to thousands of mosquitoes. Animals which can serve as effective amplifiers are usually those with large populations and rapid population turnovers. Unless the population of newly born susceptibles is large, a host cannot be an effective amplifier, e.g., horses or possibly cows in Japan. But with vertebrates such as herons and pigs, the density of infected mosquitoes can indeed be rapidly increased during early summer. The need for the host to be attractive to mosquitoes is exemplified by wild rodents in Japan which occur in large populations which turn over rapidly but apparently because they are not attractive to the vector, C. tritaeniorhynchus, JE virus is rarely carried to them to effect amplification. The involvement of rodents may be different in other areas, for example, Taiwan.

The disease hosts of JE virus are man, horses, swine fetuses and rarely other animals. Man becomes infected when the density of infected mosquitoes becomes great enough for man (who is not the preferred host of most vectors of JE virus) to receive bites of infected mosquitoes. Probably in man the infection is usually "dead end" because it is unlikely that many vector mosquitoes bite viraemic humans. At least a mosquito-man-mosquito cycle for JE virus in temperate zones is probably a much less effective amplification cycle than are mosquito-bird-mosquito or mosquito-pig-mosquito cycles.

The remaining mystery of JE virus ecology in temperate zones concerns the overwintering of virus. Perhaps JE virus overwinters in hibernating, adult female C. tritaeniorhynchus, even though the number of overwintering mosquitoes is small. This thesis is possibly supported by the high prevalence of infected mosquitoes, and by the annual recurrences of infected C. tritaeniorhynchus at the same time of year at study sites near Tokyo during 1953-1956. However, it is certainly possible that alternative cycles as yet unidentified, involving either ecto- or endo-parasites other than mosquitoes, or vertebrates other than birds or pigs, are important in interepidemic survival of JE virus. Overwintering in birds as a latent infection to be reactivated by stress of migration or hormonal changes during the spring breeding season conceivably might also occur. Although the most likely explanation for endemicity of JE virus in Japan resides in local overwintering of the virus, one cannot at this time completely eliminate the possibility of annual reintroduction of virus by migrating birds from the south. Indeed an evaluation of viral transportation by moving hosts is urgently needed.

In the tropics where adult female vector mosquitoes are present continuously, the virus probably maintains itself in nature by repeated cycles between vector mosquitoes and susceptible vertebrates. Since biting preferences of tropical vectors have not been completely delineated, it is impossible to list all tropical vertebrate amplifying hosts. However, swine are undoubtedly effective amplifiers in Singapore, and one would expect from temperate zone information, that certain birds should also be tropical amplifiers. Since

virus is continually being transmitted to man throughout the year in the tropics because infected mosquitoes are constantly present and most people live amongst high vector mosquito populations, children become infected at an early age and most adults are immune from previous inapparent infection. In such areas, large populations of susceptible humans do not usually build up to permit epidemics to occur. Of course, when large numbers of susceptible people migrate to endemic areas, epidemics can be expected. However, for indigenous populations of tropical endemic regions, sporadic encephalitis is the rule and, since cases are sporadic, they usually engender little if any notoriety and concern as a threat to public health.

The known geographic distribution of JE virus is limited to South-East Asia and the Western Pacific from Singapore and India to Japan and eastern U.S.S.R.

2.7 Diagnosis

The definite diagnosis of JE virus infection is made by isolation of the virus from tissues of diseased hosts (usually human or horse brain or swine foetuses). The frequency of virus isolation from brain is dependent on the day of illness. A high positive rate of virus isolations is obtained from brains of humans dying within five days of onset of illness and almost no isolations are successful later than the tenth day. Virus isolation is rare from cerebrospinal fluid.

The recommended sero-diagnostic procedures are the hemagglutination inhibition (HI) and complement fixation (CF) tests¹. . The virus-dilution neutralization test which is expensive in mice and inexpensive in cell culture, may not demonstrate a diagnostic rise in antibody titer because the patient often already has a high titer of neutralizing antibody when the first serum is obtained. Serum-dilution neutralization tests in cell cultures have only recently been developed and have not yet been widely used for diagnosis.

Sera should be taken at least twice, the first as early as possible and the second at the 10th-25th day of the illness. The patterns of HI and CF test results on sera from JE patients are that HI antibody appears earlier than CF antibody and lasts longer. However, since the initial serum is often taken after the 5th day of disease (when HI antibody may already be present in high titer, yet CF antibody is still at low titer), the CF test is often the more successful in demonstrating a 4-fold rise in antibody.

2.8 Treatment

There is still no antiviral agent of proven value for this disease. However, several therapeutic agents have been employed early in the disease such as a series of drugs called PANS, and human convalescent or horse hyper-immune serum. Prostigmin has been used on the grounds that it reduces the pulse rate and oedema of the nervous tissue.

¹ Details of these two tests can be found in: J. Immunol. 83, 582-593; Buescher, E. L. et al (1959); Amer. J. trop. med. 7:561-573; Clarke, D. H. and Casals, J. (1958)

In the acute stage of the disease, hyperpyrexia is a frequent problem. The use of tepid sponging, ice packs, oxygen therapy, corticosteroids and anti-pyretic drugs including salicylates, chlorpromazine and aceto-~~amino~~-phenol may be effective. Careful management and nursing of the patient are important for the maintenance of unobstructed air-passages and adequate nutrition, and for prevention and treatment of complicating bacterial infections such as pneumonia. Care of the bladder and bowels, and prevention of bedsores are also important. For frequent fits, the judicious use of anti-convulsants such as phenobarbitone is recommended.

Sequelae are treated as they arise. Physiotherapy and orthopaedic measures are used for muscular weakness or deformity, anticonvulsant drugs for fits, tranquillizers and psychotherapy for behaviour disorders. In certain cases placement in special schools or institutions for the mentally subnormal are part of the programme of management which must be carefully planned for each patient.

2.9 Control

The control of Japanese encephalitis requires the interruption of the transmission chain, animal-vector-man. Man to man transmission is not considered important.

In man, prevention of disease by active immunization is the method of choice. Passive immunisation has no application except in special situations. A safe, inexpensive vaccine of proven value is still under development. In Japan considerable attention has been paid to inactivated mouse brain vaccines during the past two decades and more recently in Korea.

Between 1954 and 1960 more than 5 million children were vaccinated in voluntary programmes with formolised mouse brain vaccine (Nakayama strain, 5% mouse brain suspension clarified by settling in the refrigerator for two weeks). Since 1957 a "revised vaccine" has been used (a 2% suspension of virus centrifuged for 30 minutes at 3000 r.p.m. before formalin treatment. The "revised" vaccine was adopted because the ordinary vaccine had been shown experimentally to provoke allergic encephalomyelitis in guinea-pigs, although it should be noted that in the extensive vaccination programme in Japan no cases of allergic encephalomyelitis in children have been observed. Since the revised vaccine when concentrated can also cause allergic encephalomyelitis in guinea-pigs, a partially purified vaccine (treatment with protaminesulphate and kaolin) has been developed but not yet used in man on a large scale.

There is some difficulty in assessing the results to date with mouse brain vaccine in Japan since it has been given to all volunteers without placebo inoculated controls, although analysis of the incidence of encephalitis shows that the attack rate in non-vaccinees has been three times higher than that in vaccinees. It is urged that properly controlled trials be held to permit a more satisfactory evaluation of inactivated mouse brain vaccines.

Chick embryo vaccines appear to be inferior to the mouse brain vaccines, because virus titres are low and immunogenicity is variable.

Also it is desirable to pursue vigorously the development of attenuated vaccines prepared from virus grown in cell cultures of porcine kidneys (primary or stable diploid strains), diploid strains of hamster embryo cells or primary cultures of chicken embryos. The problems of undesirable, adventitious viruses

sometimes present in swine kidneys or in chicken embryos (lymphomatosis virus) would have to be recognized and remedied. Provided the cell strains from porcine or hamster kidneys maintain normal chromosome numbers, they might be satisfactory for virus production after development of mass production methods.

The desirable qualities of a live attenuated virus are considered to be lack of demonstrable virulence for man and animals, genetic stability even when passaged through the mosquito body and high immunogenicity. A number of "candidate" vaccine strains are being studied in various laboratories (table 2). No trials in humans have yet been conducted and possible reversion to virulence upon mosquito transfer has not been completely evaluated.

Mosquito control is a basic method of control of Japanese encephalitis. However due to the habits of adult C. tritaeniorhynchus and their extensive breeding areas, mosquito control in areas where this species is the vector is very expensive and may be impractical at this time. In areas where mosquito control is attempted, it is suggested that further studies be undertaken to evaluate its feasibility and practicability.

Since pigs have been shown to be an important host which amplifies Japanese encephalitis virus, it is proposed that pigs should be actively immunised and that the efficacy of this measure be assessed.

3. MURRAY VALLEY ENCEPHALITIS

3.1 Definition

Murray Valley encephalitis (MVE) is a mosquito-borne virus disease of man limited to Australia and New Guinea, and is synonymous with Australian X disease. The causative virus is a member of group B and bears a close antigenic relationship to Japanese encephalitis and West Nile viruses.

3.2 Public health importance

The acute form of the disease is severe and often rapidly fatal. There is a high incidence of sequelae amongst those recovering from a severe clinical attack, with manifestations ranging from prolonged coma to partial paralysis and mental impairment. However, severe cases are relatively rare and most infections are inapparent.

During the most recent major outbreak in the Murray Valley in South East Australia in the late summer of 1951 it was estimated from serological surveys and case incidence that there was one clinically apparent case for every 700 human infections. There were 40 cases in an exposed population of 150 000 and in some areas the post-epidemic immunity rate reached 20%. The highest attack rate is in children, even in previously unexposed populations. This age incidence is similar to that of the JE epidemic in the immunologically virgin population of Guam in 1948.

Although the disease is the most severe of those known to be caused by arboviruses in Australia, it is relatively unimportant as a public health hazard. In retrospect it seems likely that there have been five outbreaks concurrently in Queensland and South East Australia during the last 46 years. Except for coastal areas, Queensland is sparsely populated and the total

TABLE 2

Virus strain & source	Method of attenuation	Host used for assay of attenuation	Stability of variant	Immunizing potency	Reversion to virulence	Multiplication in mosquitoes	Research Institute
TANAKA (Human brain)	Passed 51 times in one day eggs	Mice - 4 weeks old (partially attenuated) Mice - suckling IC (virulent)	Unstable	Mice-poor	Not known	Not known	National Institute of Health, Tokyo Japan
TANAKA (Human brain)	Passed 54 times in one day eggs and 28 times in hamster kidney cell cultures	Mice - 4 weeks old (partially attenuated) Mice - suckling (partially attenuated)	Stable in suckling mice and hamster kidney cell cultures	Mice-good	Not known	Not known	National Institute of Health, Tokyo, Japan
MUKAI (Human brain, mouse brain 3x)	Passed 10 times in primary embryo mouse skin cell cultures. Then hamster kidney cell cultures	Mice - 4 weeks old (partially attenuated) Mice - suckling IC (virulent attenuated) SC (partially attenuated)	Stable in hamster kidney cell	Not tested	Not known	Not known	Institute for Virus Research, Kyoto University, Kyoto, Japan
HOTTA (Human brain, mouse brain 7x)	Passed 78 times in hamster kidney cell cultures. Then twice at limiting dilutions	Mice - 4 weeks old (partially attenuated) Mice - suckling IC (virulent) SC (partially attenuated)	Stable in hamster kidney cell cultures	Mice - generally good	Not known	Not known	Chiba University, Chiba, Japan
OCT (Okayama C. tritac-nior hynehus suspension)	Passed many times in hamster kidney cell cultures at 24°C.	Mice - 4 weeks old (attenuated) Mice - suckling (partially attenuated) Monkeys - (partially attenuated) Chimpanzees - (no infection) Man - (? attenuated)	Stable in hamster kidney possibly unstable in some characteristics when passed in man.	Mice - good Monkeys - low Chimpanzees - none Man - under study	Not known	Not known (33rd passage)	University of Pittsburgh, Pittsburgh, U. S. A.

population at risk in the areas of the Murray River and its tributaries is probably less than 250 000. The future importance of the disease in these areas, and more particularly in the presumed areas of endemicity in the far north, would be greatly magnified if there were significant changes in the present population distribution.

3.3 Etiological agent

The virus particle is spherical with a diameter of 20-40 mu. It is inactivated by ether and sodium desoxycholate, and high titred haemagglutinin can be readily produced by acetone-ether extraction of infected suckling mouse brains.

Infectious ribonucleic acid can be produced by phenol extraction of purified and concentrated suspensions of the virus, and also by sodium desoxycholate when used in higher concentrations than in routine inactivation tests. The infectivity can also be destroyed by phospholipase, which suggests that phospholipid is of importance in the process of infection.

Although serologically most closely related to Japanese encephalitis and West Nile viruses, MVE virus shows broad reactivity with other members of group B in HI tests, and is therefore a useful reagent for serological surveys of group B virus activity.

3.4 Pathogenesis and clinical manifestations

As for Japanese encephalitis.

3.5 Laboratory diagnosis

Virus isolation can be most readily obtained from the brains of patients dying in the acute stage of the disease. Isolation should also be attempted from blood taken during the early febrile stage.

Serological diagnosis can be made from paired sera and the techniques used are the same as those for Japanese encephalitis.

Primary isolations of virus have been made on the chorioallantoic membrane of embryonated hen's eggs and highly diluted virus readily produces plaques on monolayers of avian cells. These techniques may prove to be as satisfactory for field isolation of virus as I.C. inoculation of suckling mice.

3.6 Ecology and geographical distribution

Virus has been recovered from fatal cases in the states of South Australia, Victoria, and New South Wales in the area associated with the Murray and Darling River systems, and the south coast of New Guinea near Port Moresby. Recently virus has also been recovered from pools of Culex annulirostris and Aedes normanensis collected at the Mitchell River Mission on the west coast of Cape York peninsula, Queensland.

Surveys of human sera indicate endemicity of this or closely related viruses in New Guinea and across the northern section of the Australian continent, and confirm that the occurrence of the disease in southern Australia is irregularly epidemic in nature.

Although the occurrence of a virus reservoir in southern Australia has not been entirely excluded, the current hypothesis is a bird-mosquito cycle in tropical and sub-tropical regions, and the transport south of the virus by dispersal of water birds. The southward flight of water birds is not a regular migration and, although the correlation is not complete, the irregular dispersals seem to follow abnormally high rainfall in the catchment areas of the monsoonal north. In these regions the breeding of water birds is stimulated by rain rather than by regular seasonal rhythms, and it is postulated, with some evidence, that the excess population moves south as the waters recede, carrying the virus with it. Once in the southern river system the virus is presumed to be established in the resident and visiting bird population by river-frequenting mosquitoes, probably mainly C. annuli-rostris. No evidence of inter-epidemic occurrence of virus in these areas has yet been found.

An important difference between the epidemiology of Japanese encephalitis and Murray Valley encephalitis is that horses do not display overt disease when infected with MVE, in contrast to the many cases seen during outbreaks of JE in Japan. Similarly there is no evidence of still births in swine following outbreaks of MVE. Domestic animals often have antibody after an outbreak, and as there is no lack of horses and swine in the irrigation areas of the epidemic region, it is most unlikely that occurrences in domestic stock would pass unnoticed.

3.7 Treatment and control

Little opportunity has occurred to study specific treatment and this should be based on the findings for Japanese encephalitis.

No attempts have been made to prepare vaccine, although with the small population at risk, an effective vaccine would practically eliminate the already small public health hazard. Such a vaccine would be of particular value when irrigation areas are opened up in the presumed endemic areas of the far north.

If an epidemic is recognized in its early stages in the Murray Valley, vigorously conducted mosquito abatement measures should be feasible in the areas of highest human population density, and could well abort the outbreak.

4. TICK-BORNE ENCEPHALITIS

4.1 Definition

Tick-borne encephalitis is an acute encephalomyelitis of man caused by viruses belonging to the tick-borne sub-group of group B of the arboviruses. They are transmitted by ixodid ticks and in the north-east Asian region the most important vector is Ixodes persulcatus.

4.2 Public health importance

This type of encephalitis may have a very high incidence especially in newly arrived residents in an endemic area who have had no previous contact with infected ticks. It affects those who visit forests, particularly timber workers and hunters, but also many others, including school-children. The disease has a spring-summer incidence (April to August and occasionally

early September), and has acute, subacute and inapparent forms. The first two forms can result in severe residual lesions such as paralysis of shoulders and arms. Mortality rates vary from 1 to 20% and up to half the surviving patients can have some type of residual lesion.

4.3 Etiological agent

The virus etiology of tick-borne encephalitis was established in 1937 in the U.S.S.R., where this disease was first investigated fully from the viewpoints of ecology, etiology, pathogenesis, therapy and prevention. The size of the virus is 20-30 mu. It survives for at least one year at 0°C in 50% glycerol, and, when lyophilised, it survives and remains pathogenic for many years. Its pathogenicity has been studied in a variety of laboratory and wild animals. Laboratory mice are highly susceptible by various routes, particularly the intranasal and intracerebral. The far eastern virus produces more severe disease with more frequent sequelae than the European virus.

4.4 Pathogenesis

The pathogenesis of this disease appears to be essentially similar to that of Japanese encephalitis, but the process is more severe in certain portions of the brain. Certain types of neurones, especially those which are very rich in carbohydrate are more severely damaged by the virus. Notable among them are those of the nuclei of the reticular formation, substantia nigra and the anterior horn of the cervical portion of the spinal cord.

4.5 Clinical manifestations

The clinical manifestations in the acute phase can be summarized as four syndromes:

- (1) The meningitic type has very prominent meningeal signs and symptoms, and variable mild encephalitic signs.
- (2) The meningo-encephalitic type has very prominent signs of encephalitis such as unconsciousness, various types of pseudo-bulbar signs, pyramidal signs such as Babinski and others; central paralysis may be severe and sub-cortical lesions with extrapyramidal signs occur.
- (3) The polioencephalomyelitic type has varied signs including local signs of damage to the reticular formation and the anterior horns of the cervical part of the spinal cord. It is a more serious syndrome which is usually fatal and is always associated with very severe paralysis.
- (4) The poliomyelitic type includes some signs indicated above and produces some paralysis, usually due to the involvement of the cervical part of the cord.

During the acute period of tick-borne encephalitis, varying combinations of these syndromes can occur.

4.6 Laboratory diagnosis

The tick-borne viruses in group B of the arboviruses are distinct from the other members of the group and, provided only one of these viruses occurs in a district, serological diagnosis is very satisfactory. Paired sera from a case will show a significant rise in titre in one or both of the HI and CF tests.

Virus may be isolated very early in the disease from blood and sometimes from the cerebro-spinal fluid. It can be isolated quite readily from central nervous system tissue of patients dying in the acute phase of the disease, but only rarely from those dying later.

4.7 Ecology and geographical distribution

Various tick-borne viruses capable of causing encephalitis in man have been recognized in many areas in the temperate regions of the northern hemisphere. They occur in the British Isles (loupings ill), Central Europe (central European tick-borne encephalitis), many regions of the U.S.S.R., (biphasic meningo-encephalitis and Russian spring-summer encephalitis), Korea (RSSE), Canada and the United States (Powassan). Two human cases due to a virus of this group have been recorded from Japan (Negishi).

In the north-east Asian region the main vector of the virus is the tick Ixodes persulcatus, which is a tick found on the ground in deciduous and mixed conifer and deciduous forests. In different areas the infection rates in this tick vary between 0.5-3%. In some steppe areas Dermacentor marginatus may be a vector. Large domestic mammals are commonly attacked by Dermacentor silvarum and Haemaphysalis concinna which may also be involved.

I. persulcatus is a tick whose larval form ordinarily feeds on the blood of small rodents, and whose nymph also feeds on these small rodents but more on such larger animals as rabbits and hares. The adult usually prefers large widely ranging mammals and therefore, when the opportunity arises, readily bites domestic animals and man. This tick has been found on over 100 species of birds and mammals which may be involved directly or indirectly in the cycle of the virus.

This tick may show some activity in the late summer, but cases of disease are very rare. The main biting period is during the spring and early summer so that the spring-summer incidence of the disease contrasts sharply with the later summer-autumn incidence of JE.

I. persulcatus tends to congregate along the game tracks in the forests since this is the area where it can most readily find a suitable host. When man first establishes settlements in such areas, he and his domestic animals will tend to use the same tracks as the large game animals, will be exposed to tick bite and be very liable to suffer from infection.

If a larval tick becomes infected by biting a viraemic animal, it will almost always remain infected and be capable of infecting its next host in the succeeding year as a nymph. Transovarial transmission has been shown experimentally to take place from time to time with some of these viruses in their normal host ticks. Transovarial transmission appears to occur more regularly with RSSE than with the other viruses of the group. With the occurrence of transovarial transmission, the long life of the tick and the prolonged survival of virus in ticks which have been infected at various stages in their life cycle, there appears to be no difficulty in explaining the survival of this virus, although the transmission to vertebrates only occurs during a limited part of the year.

4.8 Treatment and control

Every patient with any form of tick-borne encephalitis should be admitted to hospital. The following treatments are in current use: Specific antiserum. There are two types: (a) Hyperimmune horse serum and (b) Convalescent human serum. These are given in amounts from 10-20 ml daily for three-four days. Alternatively 6-8 ml of human gammaglobulin can be given three times a day for seven-nine days. Oxygen therapy is used and, when facilities for administration by mask are not available, 1000 ml SC can be given. 40% glucose solution with ascorbic acid is widely used intravenously. Prostigmin (1 ml of 1:1000) can be employed as anti-oedematic therapy.

Vector control can be achieved through the use of insecticides such as DDT. Effective control in the forests can be obtained by spraying along the game tracks where the ticks congregate and the effect can be very long lasting. Spraying can also be used for eliminating ticks from gardens and from domestic animals. The use of protective clothing for timber workers and others who visit forests in the endemic areas is desirable and health education is essential so that the workers may understand the value of protective measures.

Domestic animals which wander into tick infested forests tend to bring infected ticks into close contact with human habitations. Prevention of this, as by fencing, is desirable.

A formolised mouse brain vaccine is used for prophylaxis in the endemic areas. Three 1 ml SC injections of vaccine are given, the second dose ten days after the first and the third one month later. The course should be started not less than two months before the epidemic season. Booster shots are given in subsequent seasons. This vaccine has given good protection.

5. MOSQUITO BORNE HAEMORRHAGIC FEVERS DUE TO DENGUE AND CHIKUNGUNYA VIRUSES

5.1 Definition

Recent outbreaks of illness in three areas of South-East Asia caused by dengue and/or chikungunya viruses have received the names Philippine, Thai and Singapore Haemorrhagic Fevers. In their most severe form in children these diseases are characterized by haemorrhagic manifestations, shock and appreciable mortality. Infection by the causative viruses of childhood haemorrhagic fevers has been shown to cause febrile disease with rash in Asian adults and the dengue syndrome in Caucasians.

5.2 Public health importance

5.2.1 Philippines

Haemorrhagic fever in children was first described from cases admitted to Manila hospitals during the rainy season of 1954. An outbreak of approximately 750 reported cases with 10% mortality occurred in and around Manila in 1956. Since that time, 200-300 cases have been recognized in Manila hospitals yearly. In 1960, 1200 clinically diagnosed cases were reported from the Isabela region.

5.2.2 Thailand

Haemorrhagic fever in epidemic form was first recognized in 1958. Review of hospital records, however, suggests that cases have occurred in Bangkok since 1951. Epidemics have occurred during the rainy season at two-year intervals since 1958. Hospitalization figures in Bangkok for this period were: (deaths shown in parentheses) 1958, 2418 (240); 1959, 124 (?); 1960, 1742 (60); 1961, approx. 400 (?); 1962, 3741 (173) to Nov 1. In 1962, approximately 1500 hospitalized patients were reported outside Bangkok. Haemorrhagic fever in Thailand is a disease of children which is associated with a mortality rate of 5-10% and an average length of hospitalization of nine days. A large increase in serologically diagnosed non-hospitalized patients was associated with the 1962 epidemic. Virologic studies have shown that up to 50% of minor illnesses were caused by dengue or chikungunya viruses.

5.2.3 Singapore

In 1960, non-fatal dengue-like illness associated frequently with rash, petechiae and thrombocytopenia was observed in approximately 200 Asians, predominantly adults. In 1962, a more severe disease resembling the Thai and Philippine syndromes was seen in approximately 60 hospitalized children. No fatalities have been recorded thus far in virologically studied patients.

5.3 Etiology and transmission

Dengue viruses of several types and chikungunya virus have been etiologically associated with the mosquito-borne haemorrhagic fevers on the basis of serology and numerous isolations from patients and mosquitoes. At present, there is a suggestion that chikungunya virus generally produces milder disease than the dengue viruses but there is not sufficient difference for a clinical differential diagnosis to be made. The viruses involved vary according to area as follows:

Philippines - dengue 2,3,4 with dengue 3 and 4 predominating.

Thailand - dengue 1*, 2*, 3, 4, and chikungunya.

Singapore - 1*, 2*, and 4.

It is suggested that the dominant viruses may also vary from one outbreak to another in the same area.

Aedes aegypti has been incriminated as the vector of the viruses involved on the basis of epidemiological studies, and of several isolations of dengue 3, 2*, and chikungunya. It is possible that the Aedes albopictus in the Philippines and Singapore may act as a secondary vector. Some isolations of chikungunya virus have been made from Culex pipiens fatigans (Culex quinque fasciatus), but this species has not yet been demonstrated to be an important vector.

* Types 1 and 2 from Thailand and Singapore are distinct from the prototype strains and have been tentatively proposed as types 6 and 5, respectively, by Hammon, Sather and Rudnick.

5.4 Pathogenesis and clinical manifestations

The clinical description that follows is based upon observations of haemorrhagic fever in Thailand where disease experience has been the most extensive.

In its severe form haemorrhagic fever has a sequence of clinical symptoms and signs which form a distinct and readily recognizable clinical syndrome.

The illness begins with a prodromal stage characterized by fever, upper respiratory signs and symptoms and occasionally headache, vomiting and abdominal pain. This state continues for two-four days during which the child is ambulatory. It is followed by an abrupt deterioration in the patient's condition with the rapid onset of lassitude, weakness and physical collapse. Most children are brought to the hospital at this stage. On examination the child generally has cool extremities with a warm trunk, flushing of the face, restlessness, diaphoresis, petechiae located most frequently on the forehead and distal extremities and less frequently macular or maculo-papular rashes. There may be circumoral and extremity cyanosis. Systolic and diastolic blood pressures are low with a narrowing of the differential. There is marked tachycardia with weak thready pulse and faint heart sounds. The pharynx is injected. The liver is enlarged two-three finger breadths, firm and non-tender. Various changes in normal neurologic reflexes and the appearance of abnormal reflexes may be observed.

On the fourth or fifth day of illness the severely ill patient is in danger of dying. Following the period of crisis children show steady and fairly rapid improvement. Melena, haematemesis, severe ecchymoses, coma, and deepening or unresponsive shock have a grave prognosis.

Common laboratory findings are a positive tourniquet test, prolonged bleeding time, thrombocytopenia, leucocytosis with Turck cells, and haemoconcentration with increased haematocrit and haemoglobin concentration. Bone marrow shows maturation arrest of megakaryocytes. EKG shows evidence of diffuse myocardial abnormality. There is frequently X-ray evidence of right-sided pleural effusion and in severe cases biochemical evidence of liver damage.

The pathogenesis of the disease is as yet imperfectly understood. However, there is evidence of damage to blood vessels with abnormal permeability for fluids and red blood cells. There may be myocardial damage with varying degrees of right-sided failure. The combination of these mechanisms may account for the shock syndrome with fluid loss into peritoneal, pleural, pericardial and interstitial spaces and for the petechiae seen in the living patient and focal haemorrhages seen on autopsy. There is also pathological evidence of damage to liver parenchymal cells and to bone marrow. These abnormalities probably explain the abnormal blood clotting, which occurs.

Philippine haemorrhagic fever conforms generally to the above description except that epistaxis is more common and liver enlargement has not been described. The severe syndrome in children in Singapore in 1962 was similar to Thai haemorrhagic fever.

5.5 Diagnosis

No method is yet available to obtain serologic evidence of the specific infecting dengue virus type. By inoculating acute serum IC into suckling mice with 1 or 2 subsequent blind passages, dengue viruses may be isolated. Then they may be typed. At present, there is no justification for this expensive and cumbersome technique for routine diagnostic purposes since clear differences in the prognosis or the clinical syndrome have not been related to virus type.

Rapid serologic diagnosis of a group A or a group B infection may be made by using the HI test on paired sera, the first specimen obtained early in illness and the second, two weeks later. More virus-specific data may be obtained using the complement fixation test or possibly with the newly described sensitized erythrocyte agglutination test. In areas in which Japanese encephalitis is a cause of disease co-existent with dengue, the latter techniques are desirable. The HI test is most useful for detecting chikungunya virus infection in the absence of other cross-reacting group A viruses in the area.

5.6 Ecology and geographic distribution

The mosquito-borne haemorrhagic fevers are rapidly becoming epidemic diseases of considerable importance in these Regions. They are presently reported from urban areas in the Philippines, where they are widespread, Thailand and Singapore. In Thailand they are centered in the Bangkok-Dhonburi area and cases are reported as far north as Chiangmai and south to Nakhorn Srithammarat, not far from the Malayan border.

The only known cycle is an urban man-A. aegypti-man cycle. The distribution of the disease is limited by the distribution of A. aegypti, which is highly anthropophilic, is diurnal and crepuscular in activity and has a short flight range. It breeds in artificial containers and receptacles. Adults are found almost exclusively inside houses. Its seasonal distribution is not well studied but is generally considered variable. It occurs in relatively high numbers in all the areas where the disease has been reported.

The etiological agents are now probably endemic in each of the areas where they have been demonstrated. Their recent appearance in epidemics of severe disease is unexplained. Four explanations, all without supporting evidence, have been suggested: (1) introduction of the viruses from other areas, (2) variation of known viruses, (3) spread from previously-existing unknown enzootic centres, and (4) assumed epidemicity from an endemic state in which unrecognized sporadic cases occurred.

5.7 Treatment

Treatment of shock and haemoconcentration are the first therapeutic aims. Bed rest, shock position, and the administration of intravenous fluids and plasma expanders such as human plasma or salt free human albumin are employed. For severe bleeding whole fresh blood transfusion is used. Starting in 1958, steroids have been used to treat the acute stage of haemorrhagic fever in Thailand. While its efficacy has not been subjected to controlled clinical trial, use of steroids does not noticeably worsen the disease and, together with other therapeutic measures, has been associated with a decreasing mortality rate. Broad spectrum antibiotics are given to cover steroid

administration and against pneumonia. In Thailand, vitamins C and K are administered empirically. Severely ill patients must receive nutrients and fluids parenterally.

5.8 Control

1. Specific mosquito control directed against A. aegypti. Residual spraying with an appropriate insecticide is recommended.
2. Public health education with special emphasis on the habits of A. aegypti and means of preventing its breeding.
3. Quarantine of viraemic patients in screened quarters.
4. No suitable vaccine is yet available.

6. KYASANUR FOREST DISEASE

6.1 Definition

Kyasanur forest disease (KFD) is a haemorrhagic fever due to a tick-borne virus belonging to group B, which falls antigenically into the Russian spring-summer complex of viruses. Overt disease is seen in man and monkeys in nature.

6.2 Public health importance

The disease is of considerable importance within its limited distribution. Human exposure occurs during the winter when male villagers work in the forests and are bitten by infected ticks. The disease appears in November, increases during January and remains at a fairly high incidence until the gradual abatement in June. Because of its association with forest work, there are more cases in men than women, and children below the age of 10 years generally escape infection. Mortality in observed outbreaks is 5%.

6.3 Pathogenesis and clinical disease

Within about a week of exposure there is a sudden onset of headache, fever, low back and leg pains, prostration and conjunctivitis, followed in some cases by diarrhoea and vomiting. Bleeding from gums and nose is common, and a few patients have severe intestinal bleeding. Some patients display pulmonary involvement with persistent cough, which sometimes produces blood tinged sputum or frank blood. No rash is seen. There are leucopenia, lowered platelet count and albumin in the urine. The acute stage of the disease ranges from a few days to two weeks and deaths occur during this stage. Some patients suffer a second feverish period of one day to one week in duration one to two weeks after the subsidence of the acute phase.

6.4 Laboratory diagnosis

The virus is readily isolated in infant mice by IC inoculation. Hemagglutinin is prepared from mouse brain, and diagnostic serology can be carried out on paired sera as for other members of the group.

6.5 Ecology and geographical distribution

The disease was first reported in monkeys in forested areas of the Shimoga district in Mysore in 1957. The villagers had already related the monkey epizootic to a human disease associated with forest workers. Two species of monkeys, Presbitis entellus (langur) and Macaca radiata live in the forest. Animals of both species are highly susceptible and may die from the disease. Viraemias are of sufficiently high titre to infect ticks. Neutralizing antibodies have been found in several species of rodents, including the forest rats, Rattus rattus wroughtoni, and R.r. blanfordi, and the shrew, Suneus murinus. In the laboratory some of these species circulate virus in concentrations adequate to infect ticks. Neutralizing antibodies have also been found in cattle, dogs, and birds.

Ticks of the genera Haemaphysalis, Ixodes, and Amblyomma have been found in the outbreak area. The virus has been isolated from nymphs and adults of H. spinigera, and the nymphal stage of this tick is most numerous during the dry winter when human and monkey cases occur. The adult form is most prevalent at the onset of the monsoons, which coincide with a sharp decrease in the incidence of the disease. Ixodes spp. are the most common ticks on rodents, while Haemaphysalis spp. are most common on humans, monkeys and birds. The villagers in this area are in clearings in the forest surrounded by fields, and the villagers, mainly the men, go into the forest to work during the winter months when contact with infested ticks is most likely to occur.

The spread of the disease from its original focus has been extremely slow, but now the original area of infection appears to be free of the disease and is surrounded by newly invaded areas. This phenomenon implies that there is no transovarial transmission in ticks.

It was a natural assumption that infected ticks had been brought in by migratory birds from the U.S.S.R. to start this apparently isolated focus. However, migratory birds carry very few ticks and only of the local species, and KFD virus, although antigenically related, has been shown to be distinct from the other members of the RSSE virus complex.

Serological evidence suggests that KFD virus or a very closely related virus is present in Kutch and Saurashtra on the north west coast of India. Neutralizing antibodies have been found in men, horses, donkeys and camels. In this area H. intermedius is the tick most closely related to H. spinigera.

6.6 Treatment and control

As in other haemorrhagic fevers, in the event of cardiovascular collapse it is important to increase the blood volume by the use of fluids and plasma expanders.

It is probably impossible to eradicate or control the vector, and the most promising control has resulted from the use of specific formalized vaccines.

7. EPIDEMIC NEPHROSO-NEPHRITIS (KOREAN HAEMORRHAGIC FEVER)

Epidemic nephroso-nephritis is an acute haemorrhagic fever associated with renal ~~damage~~ which may be severe. The causative virus has not yet been isolated in laboratory hosts and it is far from certain that it is an arbovirus. Further it is unlikely that it is normally transmitted to man by the bite of an arthropod, although there is suggestive evidence that it is transmitted between rodents by gamasid mites. It is an important problem in the areas in which it occurs.

After an incubation period of 11-35 days, the disease has an acute onset with fever and malaise. Intestinal, uterine and nasal haemorrhages occur very commonly but, in most areas, skin petechiae are unusual. In contrast to the other haemorrhagic fevers, there may be a deterioration in the patient's condition after the temperature has fallen, due to renal failure. The mortality varies from 3-17%. At present the diagnosis rests on clinical findings.

Similar syndromes occur in Scandinavia, European Russia, patchily in the Asian part of U.S.S.R., northern continental China and Korea. Thirty-two cases with one death have recently been recorded in Osaka district in Japan. In all areas it occurs predominantly in the late autumn and early winter, but cases may occur at other times of the year in certain circumstances. Autumn is the time when murine rodents come into the houses and there is evidence that man can be infected from the fomites of these animals. There is also suggestive evidence of large scale epidemics in voles due to this condition. In Korea it has been thought that the bites of trombiculid mites may infect man, but this cannot occur in some parts of the range of the disease, because they are not active in the epidemic season.

Until further knowledge is obtained it is not possible to recommend any control measures.

8. DENGUE

8.1 Definition and public health importance

Dengue is an acute febrile disease which occurs in many areas in the tropics, sub-tropics and temperate zones. The viruses fall into group B of the arboviruses.

Epidemics may occur from introduction of the virus into any inhabited area where there is a large population of Aedes aegypti and clinical disease has occurred in up to 40% of the population. The endemic disease may be less severe than the epidemic form. Although the disease is rarely fatal it incapacitates most patients for three or more weeks and can, therefore, be a serious problem.

8.2 Clinical picture and laboratory diagnosis

It is an acute disease with an onset with fever, severe backache, frontal headache, and pains in the limbs of such severity as to lead to the common name of "break-bone fever". In the classical cases there are a rash, lymphadenopathy and varying degrees of prostration. The acute phase is characterised by "saddle-back" fever and usually lasts five to ten days, but recovery is slow and convales-

cence may be prolonged. Mild epidemics and sporadic cases may be less severe and lack the rash and intense pains. They are often difficult to differentiate clinically from influenza, therefore laboratory investigation is essential for an etiological diagnosis. Isolation of the virus is difficult and laborious and blind passages in suckling mice are usually necessary; therefore, in most cases, serological tests are the most convenient. In areas where other group B arboviruses are active it is very difficult to make a definite aetiological diagnosis by serological methods. In areas where other related viruses do not occur the diagnosis can be made on the H.I. and C.F. tests. At present, virus isolation is not a practical diagnostic method and can only be used as a research tool in studies of these viruses.

8.3 Ecology

In urban areas dengue viruses are transmitted by the bite of infected A. aegypti. Only man and this mosquito are necessarily involved in the cycle. It has been shown that monkeys of various species can be infected and develop antibodies, but there is as yet little evidence that they are involved in a sylvatic cycle of the virus. Epidemics of dengue have occurred in most parts of the tropics, sub-tropics and temperate regions where A. aegypti is found (Annexes 1, 3 and 4). Three epidemics in Japan have occurred in the absence of A. aegypti and the vector incriminated was A. albopictus. Other members of the Stegomyia sub-genus have been incriminated in other areas. The most likely explanation of this distribution is the theory that man has been the carrier who has arrived in a new area with a viraemia and has infected the local Stegomyia mosquitoes. A. aegypti is very readily introduced into areas free of this mosquito and epidemics have been associated with such introductions.

Endemic dengue is very difficult to diagnose clinically, and the diagnosis may be unjustifiably fashionable in some areas at some times and many cases of other diseases will be diagnosed as dengue. At other times many cases of dengue may be diagnosed as influenza or other diseases. To establish where endemic dengue is present virological investigations are necessary. Endemic dengue is confined to the tropics, and a number of such areas have now been defined, either by virus isolations or by serology. Their nature and location suggest that a sylvatic cycle in monkeys and some jungle Stegomyia cannot explain this phenomenon completely. It is, therefore, necessary to consider the possibility of some other wild life reservoir host or of man himself being the reservoir. Studies on these possibilities are being actively pursued, but it is difficult to believe that a virus which stimulates such long lasting antibodies could survive in relatively small populations of a long-lived, slow breeding species such as man. However, it remains theoretically possible that stress or some temporary fall of antibody level might enable a latent virus to reinvade the blood and so infect a vector mosquito and keep the cycle of the virus going.

8.4 Control

Control of urban dengue can be obtained by eradicating A. aegypti. After the 1943-44 epidemic in Australia, this mosquito was eradicated from certain large cities. When a new epidemic occurred in 1953 these cities, which had maintained their freedom from A. aegypti, were completely spared, although the case rate in smaller towns suggested that the strain of virus was as readily transmitted as any in the past.

An attenuated virus vaccine which leads to the development of neutralizing antibodies in man without causing symptoms is being studied, but has not yet been sufficiently developed for field trials to be undertaken.

9. PHLEBOTOMUS (SANDFLY) FEVER

9.1 Definition

Phlebotomus fever is an acute short-lasting pyrexial illness in man due to at least two ungrouped arboviruses, the Sicilian and Naples viruses. Only one, the Sicilian, extends from the Mediterranean littoral to the Middle East, southern U.S.S.R., Pakistan and north and central India.

Acute attacks are seldom seen in adult residents of an endemic area. The incidence in individuals newly arrived in such an area is very high.

9.2 Vector

So far as is known the Sicilian virus has no hosts other than the vector, Phlebotomus papatasi and man. There is, therefore, some difficulty in understanding the survival of this virus. However, it has been shown that the virus can be transmitted transovarially in the vector and it has been reported to pass through three generations of Phlebotomus without an infectious blood meal having been taken. It is not easy to demonstrate transovarial transmission experimentally, which clearly does not take place readily, but may be the main means of survival of the virus in a highly immune population. This is a difficult virus to isolate and work with, and no adequate experiments have been undertaken to examine the possibility of a wild-life cycle.

9.3 Control

The Phlebotomus breeds in cracks in walls and the ground and in animal burrows. The larvae feed on organic material in these sites. The control method of choice is the elimination of the insects by the use of residual insecticides on all buildings. The adults have a very limited flight range and clearing zones of 100 to 200 metres around inhabited areas is effective. It is also helpful to see that buildings are kept in good repair and that rodent population is reduced to a low level.

10. AFRICAN HORSE SICKNESS

10.1 Definition, importance and geographic distribution

African horse sickness is an acute, highly fatal epizootic disease of equines due to a number of serological types of arbovirus which do not fall into any of the existing groups.

The disease is of great economic importance in the areas in which it occurs.

The disease in India is due to a strain of virus related to the African type 6, but the African vaccine failed to protect against the Asian strain. It was isolated from the blood of horses as late as the ninth day. In Africa Culicoides species are the vectors, but no virus isolations have been obtained from them in India.

In 1959-60 the disease appeared in epizootic form in the Middle East and spread rapidly. Pakistan and India were involved. It broke out in Rajasthan (India) in April 1960. It was initially confined to this region and no fresh cases were reported there from June 1960.

In the beginning of August 1960, the disease broke out in Maharashtra rapidly spreading to several districts within the State as well as to adjoining States. Rajasthan had a second flare up of the disease and sporadic cases occurred in Punjab, Jammu and Kashmir States. It is estimated that from April to the end of 1960, approximately 22 000 horses were affected of which some 20 000 died. In 1961 there were again cases in many parts of India.

10.2 Control

An attenuated live virus vaccine has been developed which is very effective in controlling the disease, but mild and transient neurological involvement was seen in foals and yearlings three to seven weeks after vaccination. Further, in October 1960 an outbreak of encephalomyelitis occurred in 410 animals, which had been vaccinated 30 to 44 days previously and were located in three different areas. This may possibly have been caused by the vaccine.

11. VIRUSES NOT YET RELATED TO DISEASE

In the course of investigations of diseases of known public health importance numerous arboviruses have been isolated in the Regions, and have been the subject of study but have not yet been related to disease. These are listed in Annex 2; others are still at an early stage of investigation.

It is evident that several have a wide geographical distribution. Sindbis virus has been isolated in India, Malaya, Philippines, Australia and New Zealand. Antibodies have been demonstrated in man to at least eight of the 32 viruses included in Annex 2, and in other vertebrates to 11. While the antibodies detected must be viewed with caution and may be due to related viruses, known or not yet isolated, they suggest ability to cause infection. It must be considered possible therefore that some of these viruses may be of importance as causes of disease in man and/or domestic animals. This is made more likely by the recent demonstration that one of them (Sindbis) produces febrile illness in man in Africa.

Some comments may be made on individual viruses:

The Malayan viruses AMM2021 and AMM2354 have been used in diagnostic tests for Australian epidemic polyarthriti¹s. Results suggested that the agent of this disease is related to but distinct from the Malayan viruses. However, the possibility that they or their close relative, Sagiyama, may cause similar disease must be the subject of further study.

Eastern equine encephalitis virus has been isolated once from a monkey in the Philippines, and antibodies have been demonstrated in horses and carabaos. The virus has also been recovered from mosquitoes collected in Thailand. The possibility that this known pathogen may be a cause of encephalitis in the Western Pacific and South East Asian Regions must be considered.

Febrile illness, encephalitis and polyarthriti¹s of unknown aetiology are frequently described from the countries of the Western Pacific and South East Asia. It must be considered highly probable that the cause of at least some of these syndromes will be found to be arboviruses not yet linked to disease.

¹ Epidemic polyarthriti¹s. There have been several epidemics of a mild febrile illness with arthralgia and rash in Australia, most notably in northern Australia in 1942-1944, and in the Murray Valley in 1956. Attempts to isolate virus have been unsuccessful but antibody studies on paired sera suggest that the disease is carried by a group A virus related to AMM2021 and AMM2354.

The clinical features include malaise and fever rarely exceeding 38°C and arthralgia occasionally progressing to effusion in joints. In some cases there is a papulo-vesicular rash scattered over the body and limbs. The course is benign and most patients recover within seven to fourteen days, but a few cases have joint pain and swelling lasting up to several months. Some cases have rash without arthralgia.

Diagnosis by serological tests against AMM2021 or AMM2354 confirms less than 30% of cases during epidemics, and the isolation of the causative virus is needed to provide an accurate diagnostic test.

Sporadic cases of the disease have been recognised in Queensland and small epidemics have occurred between January and May each year since 1959. Antibody to group A viruses is widespread in man and other vertebrates in Australia, but how much of this is due to the virus of epidemic polyarthriti¹s is uncertain. The vector is not known.

12. CONCLUSION

The preceding sections of this report show clearly that Japanese encephalitis¹ and the haemorrhagic fevers are important public health problems in the Regions represented at this seminar. Further the evidence clearly indicates that haemorrhagic fever is an increasing problem. Classical dengue has, in the past, been an important problem and remains a permanent threat. Tick-borne encephalitis in the north of the area and Murray Valley encephalitis in the south are severe diseases which could become very serious problems if the populations in the endemic and epidemic areas were to increase substantially.

Other viruses which have been shown to be capable of causing disease in man are present, but their importance has not yet been assessed. Further there is a considerable number of other viruses, some of which are known to be capable of infecting man and/or domestic animals, whose significance as pathogens remains quite unknown.

In certain countries there is a substantial body of information about those viruses which cause serious disease and which have been recognised for several years, but in many others, in which some of these viruses have been shown to occur, their importance has not yet been fully appreciated; while in other countries, at the present time, very little objective information is available.

In view of the actual and potential importance of these viruses, further investigations should be undertaken on the following lines:

1. To obtain better understanding of the natural ecologic cycles of JE and other arboviruses present in the Regions especially those known to be human and/or animal pathogens.
2. To obtain better understanding of the defence mechanisms of man and animals against arboviruses.
3. To develop and improve control measures including those against vectors, and vaccination of man and animals.

¹ There was discussion on whether the name of the virus causing Japanese encephalitis should still be Japanese B encephalitis or whether, since von Economo's disease (A encephalitis) is no longer seen, the "B" could be omitted. In the discussion it was pointed out that the name in the Japanese language has always been "Nippon Noen" (Japanese encephalitis) and that the terms A and B have only been used in papers in other languages. A vote was taken among the Japanese workers attending the seminar on a motion that "The Members of this seminar recommend to the Sub-Committee on Arboviruses of the International Committee on Virus Nomenclature that the name "Japanese encephalitis virus" replace the name "Japanese B encephalitis virus". The motion was carried, nine voting in favour and one abstaining.

4. To recognize disease syndromes caused by arboviruses which have not yet been demonstrated to be pathogenic for man or domestic animals.
5. To extend knowledge of the geographic ranges of known arboviruses, their vectors, and vertebrate amplifying and reservoir hosts.
6. To discover new arboviruses.
7. To develop new and improved laboratory techniques to facilitate the studies listed above.

Further, fundamental studies on the physical and chemical properties of arboviruses, and on their effects on intact arthropod and vertebrate hosts, and on cultures of cells derived from these hosts, are highly desirable and may lead to practical therapeutic and control methods.

In order to carry out these activities it will be necessary in many countries to develop virus diagnostic laboratories. For this purpose it is essential to give adequate training to suitable people who will organise and staff such laboratories.

It is possible that the viruses causing the mosquito-borne haemorrhagic fevers in these Regions are pathogenic variants which are at present restricted to known endemic areas. It becomes desirable, therefore, not only to eradicate these agents where they are now prevalent but to prevent their spread into new areas. In this connection it would be highly valuable for governments to record and promptly report haemorrhagic fever cases so that other governments might begin surveillance and take appropriate control measures.

The importance of haemorrhagic fevers makes it highly desirable that a further opportunity be made for workers in the affected regions to meet to exchange information on this problem. It is, therefore, recommended that WHO consider holding a seminar, primarily on this subject in two years time.

ANNEXES

1. ARBOVIRUS INFECTIONS IN MAN
2. ARBOVIRUSES NOT YET RELATED TO DISEASE IN THE WESTERN PACIFIC AND SOUTH EAST ASIAN REGIONS
3. ARBOVIRUSES KNOWN TO CAUSE DISEASE IN THE WESTERN PACIFIC AND SOUTH EAST ASIAN REGIONS
4. ARBOVIRUSES ISOLATED TO DATE IN COUNTRIES OF THE WESTERN PACIFIC AND SOUTH EAST ASIAN REGION
5. PROVISIONAL AGENDA
6. LIST OF PARTICIPANTS, OBSERVERS AND SECRETARIAT
7. LIST OF DOCUMENTS

Country participating in the Seminar	Arbovirus infections in man ¹												Arboviruses not yet related to disease in the country
	JE	MVE	TBE	DEN	HF-D	HF-C	CH	HF-KFD	HF-NN	SIND	SSF	WN	
Australia		++		++ ⁷						+ ²			++
Cambodia	?			?			++				?		
China (Taiwan)	++			?°									++
Fiji and Samoa				+						+			
Guam	++°			++°									
Hong Kong	++			?°									
India	++			++				++		+ ³	++	++	++
Japan	++		++°	++°					?				++
Korea	++		++	?					6				
Malaya	++			++						+ ²			++
New Zealand										+ ²			+
North Borneo	+			?						8		? ⁴	
Philippines	+			++ ⁷	++					9			++
Ryukyu Islands	++			?°									++
Singapore	++			+	++		+						+
Territory of Papua and New Guinea		++		++°									+
Thailand	?5			++	++	++	++						+
U. S. S. R.	++		++						++		?		++
Viet Nam	++			+	?	?							

++	Infection proved by virus isolation
+	Infection shown only by detection of antibody
?	Infection suspected but not proved virologically
•	Infection not recognized since 1952
JE	Japanese encephalitis
MVE	Murray Valley encephalitis
TBE	tick-borne encephalitis
DEN	dengue
HF-D	haemorrhagic fever - dengue
HF-C	haemorrhagic fever - chikungunya
CH	chikungunya
HF-KFD	haemorrhagic fever - Kyasanur forest disease
HF-NN	haemorrhagic fever - nephrotoxic nephritis
SIND	Sindbis
SSF	Sicilian sandfly fever
WN	West Nile

Footnotes.

1. Symptomatic and asymptomatic infections are both included in this table.
2. In addition to presence of antibody in man, Sindbis virus has been isolated from mosquitoes.
3. In addition to presence of antibody in man, Sindbis virus has been isolated from mosquitoes, birds and mites.
4. West Nile virus disease is unrecognized, but there has been an isolation from a wild cuckoo.
5. In addition to suspected human cases of Japanese encephalitis, there has been development of specific antibodies in horses.
6. This disease is well recognized in Korea, but is not of proved viral aetiology.
7. Virus isolated in human volunteers but not identified immunologically with dengue types 1-4. However, there is recent antibody evidence of the presence of infections by dengue viruses.
8. Sindbis virus has been isolated from mosquitoes.

ANNEX 2

ARBOVIRUSES NOT YET RELATED TO DISEASE IN THE WESTERN PACIFIC
AND SOUTH EAST ASIAN REGIONS

Group	Virus	Country	Isolated from			Antibodies in		Remarks
			Vert.	Mosq.	Tick	Man	Other Verts.	
A	Sindbis	India	+	+		+	+	Known cause of disease in Africa
		Malaya		+		+		
		Philippines		+				
		Australia		+		+	+	
		New Zealand		+		+	+	
		Fiji & Samoa				+		
	Sagiyama	Japan		+		+	+	Closely related to viruses
		Okinawa		+				
	AMM 2021	Malaya		+		+		
		Australia		+		+	+	
	AMM 2354	Malaya		+		+		
	Eastern equine enceph.	Philippines	+				+	Known cause of encephalitis in N. America
		Thailand		+				
B	AMM1775	Malaya		+				
	Langat	Malaya			+		+	Related to tick-borne encephalitis group
	Kunjin	Australia		+		+	+	
	Kokobera	Australia		+		+		
	Edge Hill	Australia		+			+	
	Stratford	Australia		+				
Buny - amwera	Chittoor	Malaya		+				
		India		+				
Simbu	Sathuperi	India		+				
	Akabane	Japan		+				
Turlock	Umbre	India		+				
AMM 2549	AMM 2549	Malaya		+		+		
	AMM 2325	Malaya		+		+		
Koongol	Koongol	Australia		+			+	
	Wongal	Australia		+			+	
Ungrouped	Mag 115	Japan		+			+	Resistant to desoxycholate
	P531	Japan		+			+	DCA resistant
	IG2464	India		+				
	IG619	India			+			
	IG 673	India			+			
	IG690	India			+			
	IG700	India			+			
	IG3159	India		+				
	IG5237	India		+				
	IG7481	India		+				
	IG5139	India		+				
	Maputta	Australia		+				
	Corriparta	Australia		+			+	Resistant to desoxycholate

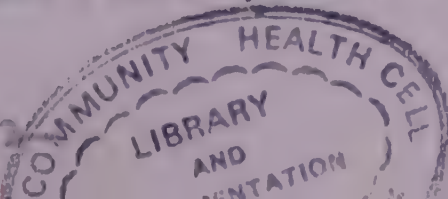
ARBOVIRUSES KNOWN TO CAUSE DISEASE IN THE
WESTERN PACIFIC AND SOUTH EAST ASIAN REGIONS

Group	Virus	Country	Isolated from				Antibodies in		Disease
			Man	Other Vert.	Mosq.	Tick	Man	Other Vert.	
A	Chikungunya	Thailand	+		+		+		Fever with arthritis or with haemorrhagic manifestations
		Cambodia	+				+		
		Singapore					+		
B	Japanese encephalitis	Japan	+	+	+		+	+	Encephalitis
		U.S.S.R.	+		+		+	+	
		Korea	+				+		
		Okinawa	+		+		+		
		Taiwan	+		+		+	+	
		Guam	+				+	+	
		Malaya	+		+		+	+	
		Singapore	+		+		+	+	
		Philippines					+	+	
		India	+		+		+	+	
		Thailand					+	+	
		Viet Nam	+				+	+	
		Hong Kong	+				+		
	dengue 1	Japan	+				+		Febrile illness sometimes with haemorrhagic manifestation
		Thailand	+				+		
		Malaya	+				+		
		Singapore	+				+		
		New Guinea	+				+		
		India	+		+		+		
		Many other countries in the region					+		
	dengue 2	New Guinea	+				+		Febrile illness sometimes with haemorrhagic manifestation
		India	+		+		+		
		Malaya	+				+		
		Thailand	+		+		+		
		Philippines	+				+		
		Singapore	+		+		+		
		Many other countries					+		
	dengue 3	Philippines	+		+		+		Haemorrhagic fever
		Thailand			+				
	dengue 4	Philippines	+				+		Haemorrhagic fever
		Singapore	+				+		
		India	+						

Antibody to dengue viruses cross react and it is not possible to allot many observations to any particular type.

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ANNEX 3

ARBOVIRUSES KNOWN TO CAUSE DISEASE IN THE
WESTERN PACIFIC AND SOUTH EAST ASIAN REGIONS

Group	Virus	Country	Isolated from				Antibodies in		Disease
			Man	Other Vert.	Mosq.	Tick	Man	Other vert.	
B	West Nile	India	+	+	+		+	+	Febrile illness some- times with encephalitis
		North Borneo		+					
	Russian spring- summer encepha- litis	U.S.S.R.	+	+		+	+	+	Encephalitis or bio- phasic fever
		Korea	+	+					
	Kyasanur Forest Disease	India	+	+		+	+	+	Febrile illness with jaundice and haemor- rage
	Negishi	Japan	+						Encephalitis
	Murray Valley Encepha- litis	Australia	+		+		+	+	Encephalitis
		New Guinea	+				+	+	
Un- grouped	Sandfly fever	U.S.S.R.	+						Febrile illness
		India	+						
	Sandfly fever (Sicilian)	Pakistan	+						
	African horse sickness	India	+						Veterinary disease

ARBOVIRUSES ISOLATED TO DATE IN COUNTRIES OF THE
WESTERN PACIFIC AND SOUTH EAST ASIAN REGIONS

Japan:	Japanese encephalitis, dengue 1, Negishi, Sagiya, Akabane, Mag115
Korea:	Japanese encephalitis, Russian spring-summer encephalitis
U.S.S.R.:	Japanese encephalitis, epidemic nephroso-nephritis, Russian spring-summer encephalitis, sandfly fever (Sicilian)
Taiwan:	Japanese encephalitis
Okinawa:	Japanese encephalitis, Sagiya
Guam:	Japanese encephalitis
Hong Kong:	Japanese encephalitis
Philippines:	Dengue 2, dengue 3, dengue 4, Sindbis, eastern equine encephalitis, P581
Thailand:	Chikungunya, dengue 1, dengue 2, dengue 3, dengue 4, eastern equine encephalitis
Vietnam:	Japanese encephalitis
Cambodia:	Chikungunya
Malaya:	Japanese encephalitis, dengue 1, dengue 2, Sindbis, AMM2021, AMM2354, AMM1775, AMM2325, AMM2549, Chittoor, Langat
Singapore:	Japanese encephalitis, dengue 1, dengue 2, dengue 4
North Borneo:	West Nile
India:	Japanese encephalitis, dengue 1, dengue 2, dengue 4, West Nile, Kyasanur Forest Disease, African horse sickness, Sindbis, Chittoor, Sathuperi, Umbre, IG2464, IG619, IG673, IG690, IG700, IG3159, IG5287, IG7481, IG5139, sandfly fever (Sicilian)
New Guinea:	Murray Valley encephalitis, dengue 1, dengue 2
Australia:	Murray Valley encephalitis, Sindbis, AMM 2021, Kunjin, Kokobera, Edge Hill, Stratford, Koongol, Wongal, Mapputta, Corriparta
New Zealand:	Sindbis

Annex 5

SEMINAR ON JAPANESE ENCEPHALITIS
AND OTHER ARBOVIRUS INFECTIONS

PROVISIONAL AGENDA

1962

<u>Date</u>	<u>Hour</u>	<u>Activity</u>
5 Nov.	9.00 a.m.	1. Opening Ceremony 1.1 Address by the Honourable Minister of Health and Welfare Message from Dr. I. C. Fang, Regional Director, WHO/WPRO Address by His Excellency, the Governor of Tokyo Address by the President, Japanese Association for Medical Sciences Address by the Vice-President, Japan Medical Association
	10.45 a.m.	1.2 Agreement on agenda and times of sessions Appointment of Chairman, Vice-Chairman and Rapporteur
	2.00 p.m.	2. Definition and classification of arboviruses (26)* 3. Public health importance of Japanese B and other arboviruses in the regions (2,4,7-10,15,16,18,20,22-25,27,28,35,38,39)
6 Nov.	9.00 a.m.	4. Ecological aspects of the problem (12,30-32) 4.1 Japanese B encephalitis 4.1.1 In cool temperate zone 4.1.2 In warm temperate zone 4.1.3 In tropical zone 4.1.4 In equatorial zone
	10.45 a.m.	4.2 Murray Valley encephalitis 4.3 Dengue 4.3.1 Classical dengue 4.3.2 Endemic dengue
	2.00 p.m.	4.4 Haemorrhagic fevers 4.4.1 Haemorrhagic dengue 4.4.2 Chikungunya 4.4.3 K.F.D. (and Langat) 4.4.4 Epidemic nephroso-nephritis 4.5 Tick-borne encephalitis

* Figures in brackets refer to the relevant working documents

PROVISIONAL AGENDA (continued)

<u>Date</u>	<u>Hour</u>	<u>Activity</u>
6 Nov.	3.45 p.m.	4.6 Phlebotomus fever
		4.7 African horse sickness
		4.8 Other viruses
7 Nov.	9.00 a.m.	5. Transmission (1, 6)
		5.1 Japanese B
		5.2 Variation of Japanese B virus
	10.45 a.m.	5.3 Other viruses
		5.4 Bionomics of Vector Mosquitoes
		6. Behaviour of Japanese B virus in Tissue cultures (17)
	2.00 p.m.	7. Japanese B as a Zoonosis (14, 19)
		7.1 Domestic animals
		7.2 Birds - Migration of Birds in Western Pacific Talk on Haemorrhagic fever - Professor Chumakov
8 Nov.	9.00 a.m.	Field visits
	2.00 p.m.	<u>Lectures:</u>
		Epidemiological pattern of Japanese B encephalitis - Dr. S. Matsuda ¹
		Treatment of Japanese B encephalitis - Dr. M. Yokota ²
		Histopathological findings of Japanese B encephalitis - Dr. M. Miyake ³
9 Nov.	9.00 a.m.	8. Pathogenesis and Clinical manifestations of arbovirus infections (29,30,46)
		8.1 Japanese B and MVE
		8.2 Tick-borne encephalitis

¹ Dr. S. Matsuda, Chief, Department of Epidemiology, National Institute of Public Health, Tokyo

² Dr. M. Yokota, Chief, Department of Internal Medicine, Tokyo Metropolitan Komagome Infectious Disease Hospital, Tokyo

³ Dr. M. Miyake, Professor, Department of Pathology, University of Tokyo, Tokyo

Annex 5

PROVISIONAL AGENDA (continued)

<u>Date</u>	<u>Hour</u>	<u>Activity</u>
9 Nov.	9.00 a.m.	8.3 Haemorrhagic fevers 8.3.1. Haemorrhagic dengue 8.3.2 Chikungunya 8.3.3 Tick-borne haemorrhagic fever 8.3.4 Epidemic nephroso-nephritis 8.4 Classical and endemic dengue 8.5 Phlebotomus fever 8.6 Other viruses
	2.00 p.m.	9. Laboratory diagnostic methods (33,36) 9.1 Serological 9.1.1 Haemagglutination inhibition test 9.1.2 Complement fixation test 9.1.3 Neutralization test 9.1.4 Reference immune serums 9.1.5 Antigen preparation 9.2 Virological 9.2.1 Collection and transport of test materials 9.2.2 Isolations of virus 9.2.2.1 Experimental Animals 9.2.2.2 Tissue culture 9.2.3 Identification and classification 9.2.3.1 Biological characteristics 9.2.3.2 Physical characteristics 9.3 Serological surveys
10 Nov.	9.00 a.m.	Consideration of report
	10.45 a.m.	9. Laboratory diagnostic methods (continued - Group)
	2.00 p.m.	9. Laboratory diagnostic methods (continued - Group)
12 Nov.	9.00 a.m.	10. Control measures (3,21,37,40) - Group discussions 10.1 Vector control 10.1.1 Alternation of breeding conditions 10.1.2 Insecticides 10.1.2.1 Insecticide resistance 10.1.3 Repellents 10.1.4 Biological control 10.2 Host control 10.2.1 Control of wild-life host populations 10.2.2 Control of domestic stock

PROVISIONAL AGENDA (continued)

Annex 5

<u>Date</u>	<u>Hour</u>	<u>Activity</u>
12 Nov.	9.00 a.m.	10.3 Vaccinations 10.3.1 Preparation and assay of formalized vaccine 10.3.1.1 Mouse brain vaccine 10.3.1.2 Chick embryo vaccine 10.3.1.3 Tissue culture vaccine 10.3.2 Development of live attenuated vaccine 10.3.3 Testing vaccines 10.3.3.1 Animal experiment 10.3.3.2 Field trial 10.3.3.3 Mass vaccination
	2.00 p.m.	Control measures - Plenary session
13 Nov.2	9.00 a.m.	11. Consideration of report
	2.00 p.m.	12. Studies to be undertaken (11) 12.1 Ecological 12.2 Defence mechanisms of man and animals 12.3 Development of control measures 12.4 New viruses 12.4.1 Discovery of new arthropod-borne viruses 12.4.2 Extension of knowledge of range of known viruses 12.4.3 Association of known "orphan" arthropod borne viruses with disease syndromes in man and animals 12.5 New laboratory techniques Address by Prof. Mitamura
	3.45 p.m.	13. International co-operation (5) 13.1 Exchange of information 13.2 Exchange of test materials
14 Nov.	9.00 a.m.	14. Final consideration of report
	2.00 p.m.	Final consideration of report - continued
	4.30 p.m.	15. Closing ceremony

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Annex 6

LIST OF PARTICIPANTS

WESTERN PACIFIC REGION

<u>Countries</u>	<u>Name of Participant</u>	<u>Title and Official Address</u>
1. Australia	Dr. Ian David <u>Marshall</u>	Department of Microbiology Australian University <u>Canberra, A.C.T.</u>
	Dr. R.L. <u>Doherty</u>	Deputy-Director Queensland Institute of Medical Research, Brisbane <u>Queensland, Australia</u>
2. Cambodia	Dr. C. <u>Chastel</u>	Laboratory Chief, Virus Laboratory Pasteur Institute <u>Phnom-penh, Cambodia</u>
3. China	Dr. <u>Lin</u> Chau-ching	Vice Director and Chief Technical Expert, Taiwan Serum and Vaccine Laboratory, 130 Fuhling Road, <u>Shihlin</u> <u>Yanminsan, Republic of China</u>
4. Hong Kong	Dr. <u>Yeoh</u> Guan-eng	c/o Director of Medical and Health Services, Medical and Health Department, Tower Court <u>Hysan Avenue, Hong Kong</u>
5. Japan	Dr. Hitoshi <u>Kasuga</u>	Technical Officer and Assistant Chief, Communicable Diseases Control Section, Public Health Bureau, 1, 2-chome Kasumigaseki, Chiyoda-ku Ministry of Health and Welfare <u>Tokyo, Japan</u>
	Dr. Mannosuke <u>Yokota</u>	Chief, Department of Internal Medicine, Tokyo Metropolitan Komagome Infectious Disease Hospital, 36 Komagome-Dosakacho Bunkyo-ku, <u>Tokyo, Japan</u>
	Dr. Shinichi <u>Matsuda</u>	Chief, Department of Epidemiology National Institute of Public Health, 1-39, Shirokanedai-machi Minato-ku, <u>Tokyo, Japan</u>
	Prof. Yosio <u>Kawakita</u>	Professor of Bacteriology Chiba University <u>Chiba, Japan</u>
6. Korea	Dr. Kyoung Ho- <u>Kim</u>	V.M.D. Chief, 3rd Section, Assay Division, National Institute of Health, <u>Seoul, Korea</u>

WESTERN PACIFIC REGION

<u>Countries</u>	<u>Name of Participant</u>	<u>Title and Official Address</u>
Korea (continued)	Dr. Chong-Hwee <u>Chun</u>	Professor, Department of Internal Medicine, College of Medicine Seoul National University <u>Seoul</u> , Korea
7. Malaya	Dr. Mohamed, <u>Din</u> Bin Ahmad	Director of Medical Services Ministry of Health Federal House, <u>Kuala Lumpur</u> Federation of Malaya
8. North Borneo	Dr. Duncan Murray <u>Cameron</u>	Invertrossachs House Near Callander, <u>Pertshire</u> Scotland
9. Philippines	Dr. Amalia L. <u>Reyes</u>	Chief of Clinics San Lazaro Hospital <u>Manila</u> , Philippines
10. Ryukyu Islands	Dr. Seiki <u>Sakumoto</u>	Chief, Dept. of Internal Medicine and Communicable Disease Section, NAHA Hospital Naha, Okinawa
11. Singapore	Prof. <u>Lim</u> Kok-Ann	Head, Department of Bacteriology University of Singapore Singapore
	Dr. <u>Phoon</u> Wai-on	Lecturer in Paediatrics University of Singapore General Hospital, Singapore-3
12. Territory of Papua and New Guinea	Dr. Frank D. <u>Schofield</u>	Director, Division of Medical Research, Department of Public Health, Port Moresby, Territory of Papua and New Guinea
13. Viet Nam	Dr. Do-chi <u>Nang</u>	Medical-biologist, Ministry of Health of Viet Nam Director of National School of Medical biology, Pasteur Institute, <u>Saigon</u> , Viet Nam

SOUTH EAST ASIAN REGION

1. India	Prof. S. L. <u>Kalra</u>	Professor of Bacteriology Bacteriology Department All India Institute of Medical Sciences, <u>New Delhi-16</u> India
2. Thailand	Dr. Prakorb Tuchinda	Chief, Division of Medical Research, Department of Medical Sciences, Ministry of Public Health, <u>Bangkok</u> , Thailand

Annex 6

LIST OF OBSERVERS

<u>Country/Organization</u>	<u>Name of Observer</u>	<u>Title and Official Address</u>
1. Far East Land Forces	Maj-General W.J. <u>Officer</u>	Director of Medical Services General Headquarters Far East Land Forces c/o GPO, <u>Singapore</u>
	Colonel M.H.P. <u>Sayers</u>	Deputy Director of Pathology Medical Directorate General Headquarters Far East Land Forces c/o GPO, <u>Singapore</u>
	Colonel T.M.W. <u>D'Arcy</u>	Deputy Director of Army Health Medical Directorate General Headquarters Far East Land Forces c/o GPO, <u>Singapore</u>
2. U.S. Naval Medical Research Unit (NAMRU-2)	Captain H. S. <u>Hurlbut</u>	MSC USN Head, Entomology Dept. U. S. Naval Medical Research Unit No. 2 <u>Taipei, Taiwan</u>
	Dr. San-pin <u>Wang</u>	NAMRU-2, <u>Taipei</u> Republic of China
3. 406 Medical General Laboratory	Major Donald S. <u>MacNair</u>	Acting Chief, Medical General Laboratory (406) APO 343 (Camp Zama), <u>San Francisco</u> California
4. U. S. Army Research and Development Group (Far East)	Colonel Arvey C. <u>Sanders</u>	Commanding Officer, U.S. Army Research and Development Group APO 343 (Camp Zama) <u>San Francisco</u> California
5. SEATO Medical Research Unit	Dr. Scott B. <u>Halstead</u>	Chief, Virology Department SEATO Medical Research Laboratory c/o Royal Thai Army Institute of Pathology, Rajavithi Road <u>Bangkok, Thailand</u>
6. Institute for Medical Research	Dr. Albert <u>Rudnick</u>	Virus Division Institute for Medical Research <u>Kuala Lumpur</u> , Federation of <u>Malaya</u> , and International Center for Medical Research and Training Hooper Foundation University of California School of Medicine <u>San Francisco</u>

<u>Country/Organization</u>	<u>Name of Observer</u>	<u>Title and Official Address</u>
7. U. S. Army Medical Service Group	Lt. Colonel S.C. <u>Gallup</u>	Lt. Col. MC 057019 Preventive Medicine Officer US Army Ryukyu Islands USA Medical Service Group <u>Okinawa, Ryukyu Islands</u>
8. First Cavalry Division, San Francisco, California	Captain A.H. <u>Unger</u>	Preventive Medicine Officer HQ 1st Cavalry Division APO 24 San Francisco, California
9. 6332nd USAF Dispensary	Colonel Paul V. <u>Davis</u>	6313th Air Base Wing (PACAF) APO 239, San Francisco California
10. Pasteur Institute	Dr. Daniel <u>Beytout</u>	Chief, Virus Laboratory Pasteur Institute of Saigon <u>Saigon, Vietnam</u>
11. Japan	Professor Minoru <u>Matsumoto</u>	Infectious Disease Research Institute, 1-39 Shirokanedai-machi Minato-ku, <u>Tokyo</u> Japan
	Dr. Yukishige Kanda Inoue	Associate Professor of Virology Institute for Virus Research, Kyoto University <u>Kyoto, Japan</u>
	Dr. Keizo <u>Ishii</u>	Section of Infectious Disease Tokyo Municipal Ebara Hospital, <u>Tokyo</u> Japan
	Dr. Hikokichi <u>Tsubahara</u>	National Institute of Animal Health <u>Tokyo, Japan</u>
	Prof. Manabu <u>Sassa</u>	Infectious Disease Research Institute, 1-39, Shirokanedai-machi Minato-ku, <u>Tokyo</u> Japan
	Dr. Hiroshi <u>Ogonuki</u>	Chiba Serum Research Institute, <u>Chiba</u> Japan

LIST OF CONSULTANTS

Dr. Masami <u>Kitaoka</u>	Chief, Department of Virology and Rickettsiology National Institute of Health 284 Kamiosaki-chojamaru Shinagawa-ku, <u>Tokyo</u> Japan
Dr. N.I. <u>Grashchenkov</u>	Professor of Neurology First Moscow University, and Member of Medical Academy of USSR <u>Moscow</u>
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